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Deprotonative Functionalization of the Difluoromethyl Group

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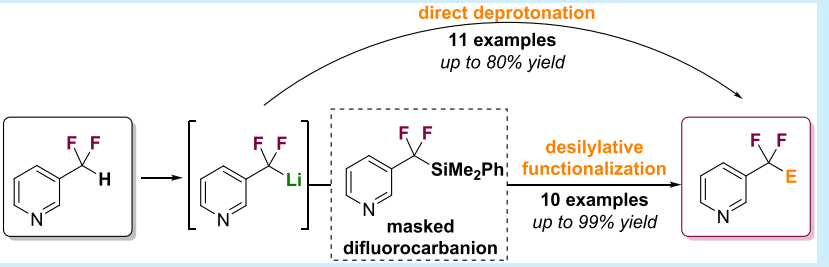

ABSTRACT: The functionalization of 3-(difluoromethyl)pyridine has been developed via direct deprotonation of -CHF_2 with a lithiated base and subsequent trapping with various electrophiles in THF. *In situ* quenching gives access to 3-pyridyl-CF_2-$SiMe_2Ph$ as a new silylated compound, which can be postfunctionalized with a fluoride source to obtain a larger library of 3-(difluoroalkyl)pyridines that could not be accessed via direct deprotonation.

It is today well-established that the introduction of fluorine atoms or fluorinated functional groups can have a profound impact on the physical, chemical, and biological properties of molecules.[1−7]

The -CHF_2 group has been increasingly studied over the past few years as its interesting properties are essential for the development of new bioactive molecules. Aside from the usual characteristics shared with other fluorinated substituents, the -CHF_2 moiety is a lipophilic bioisostere of hydroxy, sulfanyl, and amino groups, and its action has been demonstrated as that of an unusual hydrogen bond donor that can influence intramolecular interactions and conformational preferences.[8−14] The potential of this group led to a plethora of syntheses for introduction of the -CHF_2 moiety as a terminal group in heteroaromatic molecules.[15,16]

The parent difluoromethylene linkage is an attractive structural motif in drug design and agrochemistry due to its bioisosteric relationship with the carbonyl or oxygen atom.[8] Unfortunately, in contrast to the -CHF_2 group, its synthetic access remains underdeveloped and relies on the use of toxic, explosive reagents prohibited for an industrial application (e.g., DAST).[17] An attractive approach is the late-stage functionalization of the -CHF_2 moiety and, more precisely, its deprotonation followed by electrophilic trapping (Scheme 1). In the case of pyridines, the frequently encountered core in agrochemical research,[18,19] only one example of direct deprotonation of 2-(difluoromethyl)pyridine has been reported without success (a).[20] The functionalization of difluoromethyl heteroarenes has been scarcely reported, presumably because of the poor stability of the generated difluoromethyl carbanion leading to the corresponding fluorocarbene.[21,22] In the presence of a lateral directing group, the deprotonation of 2-(difluoromethyl)pyridine succeeded with better yields (b).[23] However, highly functionalized starting materials were employed, which limited the scope of the reaction. Additionally, this strategy requires further steps for the installation and the removal of the directing groups. In 2018, a breakthrough was achieved by Szymczak *et al.*, by employing hexamethylborazine ($B_3N_3Me_6$) as a Lewis acid for the stabilization of the difluoromethyl carbanion, before electrophilic trapping (c).[24] Although this versatile methodology was applied to 3-(difluoromethyl)-pyridine, a drawback for large scale application is the use of the high-cost Lewis acid and the purification step of the compound bearing the borazine.

Related to our ongoing work in developing industrially viable approaches to emergent fluorinated substituents, we were also interested in functionalizing the difluoromethyl group by deprotonation, relying on cheap, easy to handle organometallic bases such as LDA. However, the instability of the generated CF_2^- intermediate would be an issue, as mentioned above. Therefore, we decided to study first the reaction under kinetic control using *in situ* trapping conditions to avoid α-elimination of fluoride,[21,22] with commonly used

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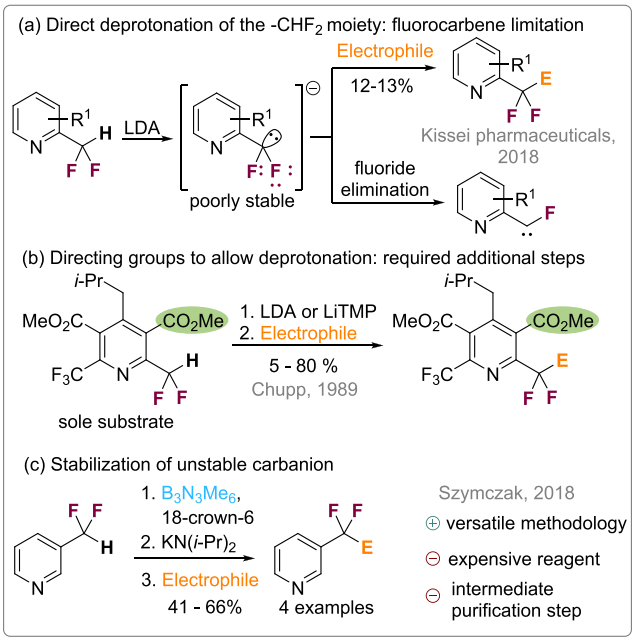
Scheme 1. Functionalization of *gem*-Difluorinated Heterocycles through Deprotonation of -CHF_2



TMSCl (Table 1). In addition, this would lead to difluoromethyl surrogates, namely (Het)ArCF_2SiMe_3, poorly available so far, which are an economic alternative to borazines. Those ideal masked (Het)ArCF_2^- anions could be used for further transformations in analogy to the Ruppert−Prakash reagent.[25−28] We focused our studies on 3-(difluoromethyl)-pyridine, which have hitherto been poorly described. When the substrate was added to a mixture of 2 equiv of LDA and 1 equiv of TMSCl as an electrophile at −78 °C, 77% of silylated **2a** was obtained, whereas a reverse or equimolar ratio of base and electrophile led to lower yields (Table 1, entries 1−3). We were quite satisfied with these results, compared to Szymczak's observation that the use of LDA on $PhCF_2$-H afforded low yields and mainly *α*-defluorination.[24] When the temperature was increased (entries 5 and 6), the yield dropped drastically certainly due to rapid degradation of the difluoromethyl carbanion above −78 °C.[21] When the bulkier LiTMP was used, only 10% of **2a** were produced albeit with 19% of the recovered starting material as well as numerous side products. We investigated also other bases like the mixed base LDA/*t*-BuOK (entry 9) and KHMDS (entry 10), which revealed inefficient. On the contrary, we also considered the non-ionic Schwesinger superbase P_4-*t*-Bu, described to successfully

Table 1. Optimization of the Reaction Conditions of *In Situ* Quenching[a]

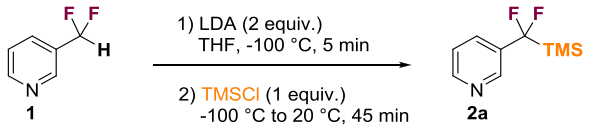
entry	base	temp (°C)	yield of **2a** (%)	recovery of **1** (%)
1[b]	LDA	−78	61	25
2	LDA	−78	77	0
3[c]	LDA	−78	55	52
4[d]	LDA	−78	74	0
5	LDA	−50	16	31
6	LDA	−30	0	36
7	LDA	−100	54	0
8	LiTMP	−78	10	19
9	LDA/*t*-BuOK	−78	NR	99
10	KHMDS	−78	NR	100
11	P_4-*t*-Bu	−78	33	60
12[e]	LDA	−78	76 (**2b**)	0
13[f]	LDA	−78	23 (**2c**)	0

[a]Reaction conditions: **1** (1.92 mmol) in THF (14 mL) under Ar. Yields reported are ^{19}F NMR yields using fluorobenzene as an internal standard. [b]With 1 equiv of LDA. [c]With 2 equiv of TMSCl. [d]At −78 °C for 2 h. [e]$Me_2PhSiCl$ was used as the electrophile. [f]*t*-$BuMe_2SiCl$ was used as the electrophile.

generate fluorinated carbanions, because of the strong destabilization of the $[P_4$-*t*-Bu/H$]^+$ F^- ion pair disfavoring *α*-elimination of fluoride.[29,30] In our hands, the yield was moderate in comparison to that obtained with LDA (33%, entry 11). The amount of recovered **1** could arise from the demonstrated activation of organosilicons by P_4-*t*-Bu.[31,32] Two other silylated electrophiles were assessed with LDA. $Me_2PhSiCl$ gave a comparable yield in contrast to *t*-$BuMe_2SiCl$, which afforded 23% of **2c** in accordance with the literature.[33]

Although these results were quite gratifying, the *in situ* trapping strategy is expected to have a limited scope as used electrophiles have to be compatible with the lithiated base.[34,35] We therefore decided to perform the reaction under sequential trapping conditions (Scheme 2).

Scheme 2. Approach to a Sequential Quench



When once again LDA was used as the base and TMSCl as the electrophile at −78 °C, the desired product **2a** was obtained with a low yield of 35%. When the temperature was decreased to −100 °C, it was possible to obtain **2a** in 80% yield, thus with the same efficiency as under the best *in situ* quench conditions. With regard to other lithium bases, no formation of **2a** was observed with PhLi, *n*-BuLi, *s*-BuLi, or *t*-BuLi. When mixed bases were assessed again, such as LDA/*t*-BuOK or TMPMgCl·LiCl, a complex mixture of fluorinated compounds was obtained (see the Supporting Information for details).

With these optimized conditions, using LDA as the base, we studied the scope of the reaction with various electrophiles (Scheme 3). Like the *in situ* quench strategy, TMSCl and $Me_2PhSiCl$ gave high yields [≤80% NMR yield for **2a** (Scheme 3)] compared to *t*-$BuMe_2SiCl$, which afforded 21% of **2c**. The (deuterodifluoromethyl)pyridine **2d** was obtained in 49% yield

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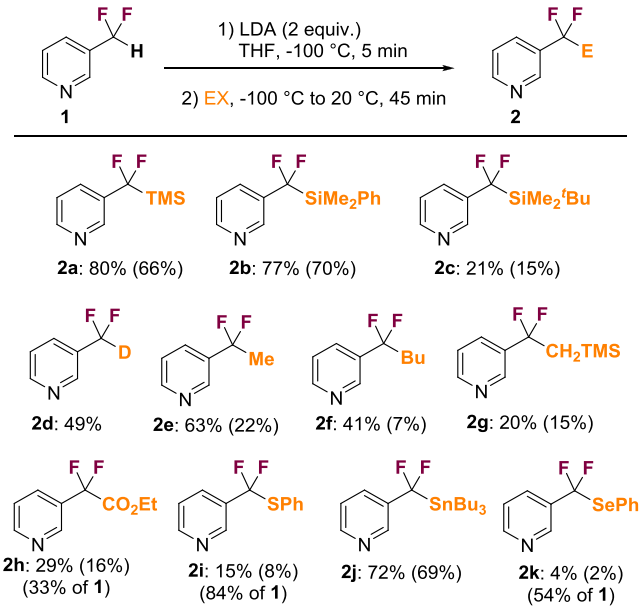
Scheme 3. Scope of Electrophiles for a Sequential Quench[a]



[a]^{19}F NMR yields were calculated with fluorobenzene as an internal standard. Isolated yields are in parentheses.

when using *in situ*-formed DCl as the electrophile. MeI gave a satisfactory 63% yield of **2e**. Alkyl halide electrophiles such as BuI and $TMSCH_2Cl$ provided full conversion but with low to moderate yields of the desired compounds **2f** and **2g**, respectively. Ethyl chloroformate, which allowed the introduction of a carboxylic moiety, gave a yield of **2h** of 29%. Although frequently employed in polar organometallic chemistry, diphenyl disulfide gave only a very poor yield of **2i** (15%). In a similar manner, phenylselenyl chloride afforded 4% of **2k**. Conversely, stannane **2j** was obtained in good yield after trapping with tributyltin chloride and would prove to be highly useful for further transformation by Stille cross-coupling to afford new Het-CF_2-Ar derivatives.[36]

Complementary to the scope of the sequential trapping conditions, we then focused on a third strategy, in which difluorosilylated products were used as masked difluoromethyl carbanions. Relieved from the concern of potential α-defluorination of the carbanion, higher temperatures can be used to increase the scope and yields. As a proof of concept, we investigated the reaction of **2b** with benzaldehyde, an electrophile that proved to be unsuccessful under lithiation conditions (Table 2).

To our delight, **2l** was obtained using stoichiometric amounts of fluoride, either TBAT or TMAF, with a moderate yield (Table 2, entries 1 and 2). When the amount of TBAT or TMAF in THF was decreased, the reaction slowed (entries 4 and 5). KF as the fluoride source was revealed to be inefficient in THF due to solubility problems (entry 3). However, when DMF was used as a solvent, a higher yield and a faster reaction were observed with a catalytic amount of KF (entry 6). In fact, the Lewis basic activation of silicon by the solvent for fluoroalkyl transfer has already been reported by Amii *et al.* in the absence of any fluoride source.[37] Accordingly, when the mixture of **2b** and benzaldehyde was heated to 90 °C in the absence of fluoride, full conversion was obtained, with formation of 23% of product **2l** (entry 8). When DMF was used as the solvent in the presence of TBAT or TMAF as the

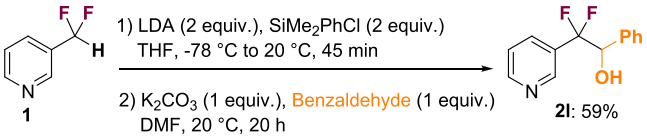
Table 2. Optimization of Reaction Conditions for the Formation of Difluoromethylalcohol 2l from 2b[a]

entry	F^- source (equiv)	solvent	time (h)	yield of **2l** (%)
1	TBAT (1)	THF	1	57 (52)
2	TMAF (1)	THF	1	59 (43)
3	KF (1)	THF	18	NR
4	TBAT (0.1)	THF	14	71 (56)
5	TMAF (0.1)	THF	48	54 (47)
6	KF (0.1)	DMF	3	64 (53)
7	–	DMF	24	traces
8[b]	–	DMF	18	23
9	TBAT (0.1)	DMF	0.5	99 (81)
10	TMAF (0.1)	DMF	0.5	51 (39)

[a]Reaction conditions: **2b** (0.5 mmol), benzaldehyde (0.5 mmol) in solvent (9 mL) at 20 °C under Ar. Yields reported are ^{19}F NMR yields using fluorobenzene as an internal standard. Isolated yields are in parentheses. [b]The reaction mixture was heated to 90 °C. TBAT stands for $[n\text{-}Bu_4N^+,F_2Ph_3Si^-]$, TMAF for $[Me_4N^+,F^-]$.

fluoride source (entries 9 and 10), the reaction was complete after 30 min at 20 °C, affording an excellent yield of 99% with TBAT (entry 9). The structure of the newly prepared (3-pyridyl)difluoromethyl carbinol was confirmed by single-crystal X-ray diffraction. We next investigated a one-pot strategy, to avoid the purification step of silylated species **2b** (Scheme 4). The direct functionalization of 3-difluoromethyl-

Scheme 4. One-Pot Strategy



pyridine **1** with benzaldehyde was achieved using K_2CO_3 in DMF affording **2l** in a gratifying yield of 59% (see the Supporting Information for details).

Next, we studied the use of other electrophiles as a proof of concept of this strategy.

With the best conditions for benzaldehyde (Table 2, entry 9), other electrophiles that were inefficient toward metalation with lithiated bases finally afforded good to moderate results, namely, 4-chlorobenzaldehyde (**2m**, 72% NMR yield), 2,4-dichlorobenzaldehyde (**2n**, 80% NMR yield), tosylated aldimine (**2o**, 47% NMR yield), benzylidenemalononitrile (**2p**, 28% NMR yield), diphenyl disulfide (**2i**, 65% NMR yield), phenylselenyl chloride (**2k**, 55% NMR yield), cyanogen bromide (**2q**, 52% NMR yield), and menthyl sulfinate (**2r**, 41% NMR yield). Only ethyl chloroformate (**2h**, 26% NMR yield) gave a similar yield as under sequential deprotonation (Scheme 5). Using the silicon-based strategy, the difluoro derivative of pyrifenox, a fungicide inhibiting ergosterol biosynthesis, was easily obtained for the first time in four steps with an overall unoptimized yield of 19% (Scheme 6).

In conclusion, direct deprotonation of 3-(difluoromethyl)-pyridine was developed for the first time via either *in situ* trapping with chlorosilanes or sequential trapping with various electrophiles after metalation of the difluoromethyl group with LDA. The newly created difluoro(3-pyridyl)methylsilanes can then react as masked difluorocarbanions and add to C=O, C=C, S−S, S−O, Se−Cl, and C=N bonds. This methodology was successfully adapted to a one-pot procedure

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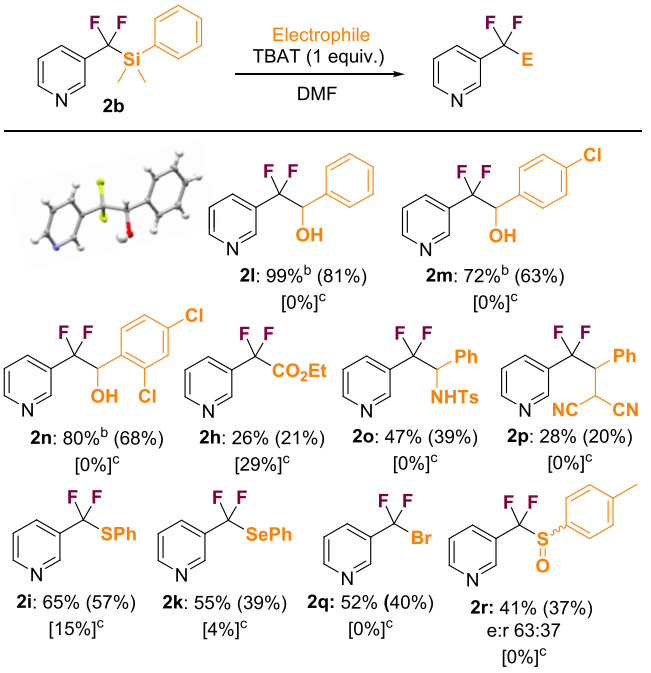
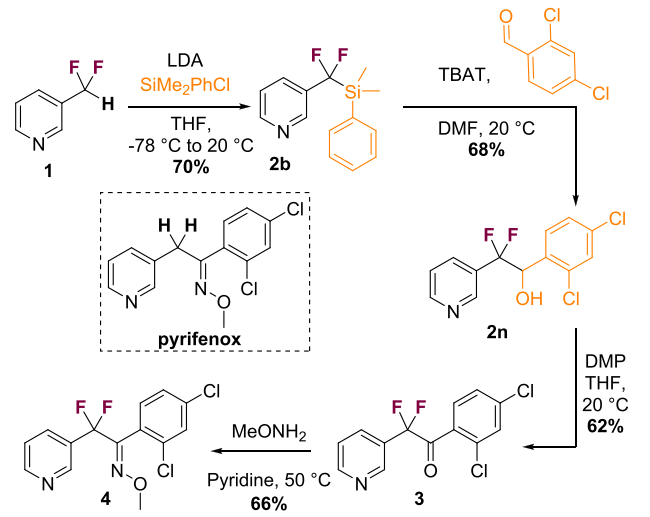
Scheme 5. Scope of the Desilylative Functionalization of Difluoro(3-pyridyl)methane[a]



[a]Yields reported are ^{19}F NMR yields using fluorobenzene as an internal standard. Isolated yields are in parentheses. [b]With 0.1 equiv of TBAT. [c]Yields obtained from sequential trapping.

Scheme 6. Synthesis of a Difluoro Derivative of Pyrifenox



affording novel HetAryl-CF_2-R building blocks based on an operationally simple and cheap methodology.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c03380.

Optimization of sequential trapping, X-ray data, experimental procedures, and characterization data (PDF)

Accession Codes

CCDC 2017677 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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